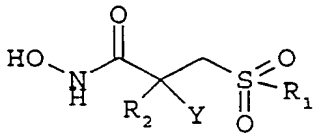
CLAIMS

We claim:

1. A compound of formula I



I

or pharmaceutical acceptable salts thereof wherein:

R_1 is

a) C_{4-12} alkyl,

b) C_{4-12} alkenyl,

c) C_{4-12} alkynyl,

d) $-(CH_2)_h-C_{3-8}$ cycloalkyl,

e) $-(CH_2)_h$-aryl,

f) $-(CH_2)_h$-het,

R_2 is

a) C_{1-12} alkyl,

b) C_{2-12} alkenyl,

c) C_{2-12} alkynyl,

d) $-(CH_2)_h-C_{3-8}$ cycloalkyl,

e) $-(CH_2)_h-C_{3-8}$ cycloalkenyl,

f) $-(CH_2)_h$-aryl,

g) $-(CH_2)_h$-het,

h) $-(CH_2)_h$-Q,

i) $-(CH_2)_i$-Q or $-(CH_2)_i$-X-R_4, optionally the $-(CH_2)_i-$ chain can be substituted with one or two C_{1-4} alkyl or phenyl, which in turn can be substituted with one to three halo or C_{1-4} alkyl, or

l) $-(CH_2)_hCHR_5R_6$;

R_3 is

a) H,

b) C_{3-6} cycloalkyl,

c) C_{1-4} alkyl, or

d) $-(CH_2)_h$-phenyl;

X is

a) -O-,
b) -S(=O)j-,
c) $-NR_7-$,
d) $-S(=O)_2NR_8-$, or
e) -C(=O)-;

R_4 is

a) H,
b) C_{1-8} alkyl,
c) $-(CH_2)_h$-phenyl, or
d) $-(CH_2)_h$-het;

R_5 is

a) C_{1-4} alkyl, or
b) $-C(=O)R_3$;

R_6 is

a) $-C(=O)R_3$, or
b) $-(CH_2)_hC(=O)R_3$;

R_7 is

a) H,
b) C_{1-4} alkyl,
c) $-(CH_2)_h$-phenyl,
d) $-C(=O)-R_3$,
e) $-S(=O)_2R_3$, or
f) $-C(=O)OR_3$;

R_8 is

a) C_{1-4} alkyl, or
b) $-(CH_2)_h$-phenyl;

Y is

a) -OH,
b) $-NR_9R_{10}$, or
c) fluoro;

R_9 and R_{10} are the same and different and are

a) H,
b) $-C(=O)-R_3$,
c) $-C(=O)-OR_3$, or
d) $-C(=O)-NHR_3$;

aryl is monocarbocyclic, or bicarbocyclic aromatic moiety;

het is 5- to 10-membered unsaturated monomonocyclic or bicyclic heterocyclic moiety having one to three atoms selected from the group consisting of oxygen, nitrogen, and sulfur;

Q is 5- to 10-membered saturated monocyclic or bicyclic heterocyclic moiety having one to two atoms selected from the group consisting of oxygen, nitrogen, and sulfur;

aryl, het, C_{1-12} alkyl, C_{1-4} alkyl C_{2-12} alkenyl, C_{2-12} alkynyl, -C_{3-8} cycloalkyl, -C_{3-8} cycloalkenyl, Q and phenyl being optionally substituted;

h is 0, 1, 2, 3, 4, 5, or 6; i is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; j is 0, 1, or 2; and

with the following provisos:

a) where R_2 is C_{1-6} alkyl, Y is other than $-NR_9R_{10}$,

b) where *h* is 0, het is attached to the α-position via carbon atom of heterocyclic moiety, and

c) where *h* is 0, Q is attached to the α-position via carbon atom of heterocyclic moiety.

2. A compound of formula I according to claim 1 wherein

R_1 is

a) C_{4-10} alkyl,

b) $-(CH_2)_h$-aryl, or

c) $-(CH_2)_h$-aryl substituted with C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, 4-chlorophenyl, O-phenyl, het, O-het, halo, $-NO_2$, $-CF_3$, -CN, or $-N(C_{1-4}\ alkyl)_2$;

R_2 is

a) $-(CH_2)_h$-Q, or $C(CH_3)_2$-Q or

b) $-(CH_2)_i$-X-R_4, $C(CH_3)_2$-X-R_4 ;

X is

a) $-S(=O)_j$-,

b) $-NR_7$-;

R_4 is

a) H,

b) C_{1-8} alkyl,

c) $-(CH_2)_h$-phenyl,

d) $-(CH_2)_h$-phenyl substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, C_{1-4} phenoxy, het, halo, $-NO_2$, or -CN, or

e) $-(CH_2)_h$-het;

R_7 is

a) -C(=O)-R_3;

Y is

a) -OH;

R_3, aryl, het, Q, *h*, *i*, *j* are as defined above, and with the proviso that where *h* is 0, Q is attached to the α -position via carbon atom of heterocyclic moiety.

3. A compound of formula I according to claim 1 wherein

R_1 is

a) $-(CH_2)_h$-phenyl, or

b) $-(CH_2)_h$-phenyl substituted with C_{1-4} alkoxy, phenyl, 4-chlorophenyl, O-phenyl, O-(pyrid-4-yl) or halo;

R_2 is

a) $-(CH_2)_i-S(=O)_2-R_4$, or

b) $-(CH_2)_i-NHR_7$;

R_4 is

a) C_{1-8} alkyl,

b) $-(CH_2)_h$-phenyl, or

c) $-(CH_2)_h$-phenyl substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, C_{1-4} phenoxy, or halo;

R_7 is

a) $-C(=O)C_{1-4}$ alkyl,

b) $-C(=O)C_{3-6}$ cycloalkyl,

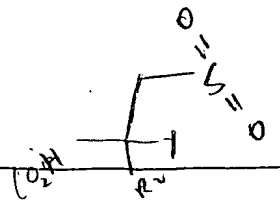
c) $-C(=O)(CH_2)_h$-phenyl, or

d) $-C(=O)-(CH_2)_h$-phenyl substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, or halo;

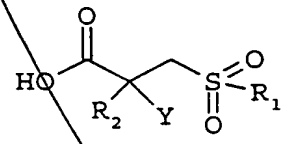
Y is

a) -OH;

and *h* and *i* are as defined above.



4. A compound of formula 8



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or pharmaceutical acceptable salts thereof wherein R_1 , R_2 and Y are as defined in claim 1.

5. A compound of claim 1 which is

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-phenylbenzenesulfonyl)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-fluorobenzenesulfonyl)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-n-butylbenzenesulfonyl)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(N-benzenecarbonylamino)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-[N-(cyclopentylcarbonyl)amino]-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl) methyl]-3-(N-(4-methoxybenzenecarbonyl)amino)-propionamide,

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-methoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-methoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-butoxy-benzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-butoxy-benzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-butoxy-benzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(methylthio)methyl-3-(4-butoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(phenylthio)methyl-3-(4-butoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-(4-butoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(pyrid-2-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(2-methyl-5-oxo-6-hydroxy-2,5-dihydro-1,2,4-triazin-3-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(2-aminothiazol-5-yl)thiomethyl-3-(4-butoxy-benzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(2-methyl-1,3,4-thiadiazol-5-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methyl-1H-imidazol-2-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methyltetrazol-5-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(tetrazolo[1,5-b]pyridazin-6-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(pyrid-2-yl)methylthiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methyl-1H-imidazol-2-yl)methylthiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-benzyl-1H-imidazol-2-yl)methylthiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(5-methylisoxazol-3-yl)methylthiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(2-benzylthio-2-methylethyl)-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(pyrid-2-yl)thio-2-methylethyl]-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(phenylthio)methyl-3-(4-chlorobiphenylsulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-(4-chlorobiphenylsulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(pyrid-2-yl)methylthiomethyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(5-methylisoxazol-3-yl)methylthiomethyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(1-methylhydantoin-3-yl)-2-methylethyl]-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(pyrid-2-yl)thio-2-methylethyl]-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-benzylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(phenylthio)methyl-3-(4-phenoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-(4-phenoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(pyrid-2-yl)methylthiomethyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methyl-1H-imidazol-2-yl)methylthiomethyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(1-methylhydantoin-3-yl)-2-methylethyl]-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(1-methyl-1H-imidazol-2-yl)thio-2-methylethyl]- (4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)-benzenesulfonyl]propionamide;

N-Hydroxy-2-hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)-benzenesulfonyl]propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]propionamide;

N-Hydroxy-2-hydroxy-2-(phenylthio)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]-propionamide;

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]-propionamide;

N-Hydroxy-2-hydroxy-2-(2-benzylthio-2-methylethyl)-3-[4-(pyrid-4-yl)-benzenesulfonyl]-propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)oxybenzenesulfonyl]propionamide or

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-[4-(pyrid-4-yl)oxybenzenesulfonyl]propionamide.

6. A compound of claim 4 which is:

2-Hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-butoxybenzenesulfonyl)-propionic acid;

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-butoxybenzene-sulfonyl)propionic acid;

2-Hydroxy-2-(phenylthio)methyl-3-(4-butoxybenzenesulfonyl)propionic acid;

2-Hydroxy-2-(benzylthio)methyl-3-(4-butoxybenzenesulfonyl)propionic acid;

2-Hydroxy-2-(2-benzylthio-2-methylethyl)-3-(4-butoxybenzenesulfonyl)-propionic acid;

2-Hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)-propionic acid;

2-Hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)-propionic acid;

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-chlorobiphenyl-sulfonyl)propionic acid;

2-Hydroxy-2-(phenylthio)methyl-3-(4-chlorobiphenylsulfonyl)propionic acid;

2-Hydroxy-2-(benzylthio)methyl-3-(4-chlorobiphenylsulfonyl)propionic acid;

2-Hydroxy-2-(pyrid-2-yl)thiomethyl-3-(4-chlorobiphenylsulfonyl)propionic acid;

2-Hydroxy-2-(5-methylisoxazol-3-yl)methylthiomethyl-3-(4-chlorobiphenyl-sulfonyl)propionic acid;

2-Hydroxy-2-[2-(1-methylhydantoin-3-yl)-2-methylethyl]-3-(4-chlorobiphenyl-sulfonyl)propionic acid;

2-Hydroxy-2-(2-benzylthio-2-methylethyl)-3-(4-chlorobiphenylsulfonyl)-propionic acid;

2-Hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)-propionic acid;

2-Hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)-propionic acid;

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-phenoxybenzene-sulfonyl)propionic acid;

2-Hydroxy-2-(phenylthio)methyl-3-(4-phenoxybenzenesulfonyl)propionic acid;

2-Hydroxy-2-(benzylthio)methyl-3-(4-phenoxybenzenesulfonyl)propionic acid;

2-Hydroxy-2-[2-(1-methylhydantoin-3-yl)-2-methylethyl]-3-(4-phenoxy-benzenesulfonyl)propionic acid;

2-Hydroxy-2-[2-(1-methyl-1H-imidazol-2-yl)thio-2-methylethyl]- (4-phenoxy-benzenesulfonyl)propionic acid;

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)benzene-sulfonyl]propionic acid;

2-Hydroxy-2-(phenylthio)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]propionic acid or

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)oxy-benzenesulfonyl]propionic acid.

7. A method of inhibiting excess matrix metalloproteinase which comprises administering to a patient in need thereof an effective amount of a compound of claim 1.

8. A method of claim 7 wherein matrix metalloproteinases comprises stromelysin, collagenase, and gelatinase.

9. A method of treating a human suffering from or susceptible to diseases involving connective tissue degradation which comprises administering to a patient in need thereof an effective amount of a compound of claim 1.

10. A method of claim 9 wherein the diseases related to connective tissue degradation are osteoarthrits, rheumatoid arthritis, septic arthritis, and osteopenias such as osteoporosis, tumor metastasis (invasion and growth), periodontitis, gingivitis, corneal ulceration, dermal ulceration, gastric ulceration, inflammation, or asthma.

11. The method of claim 7 wherein the effective amount of the compound ~~of claim 1~~ is administered orally, parenterally, or topically in a pharmaceutical composition.

12. The method of claim 9 wherein the effective amount of the compound ~~of claim 1~~ is administered orally, parenterally, or topically in a pharmaceutical composition.

13. The method of claim 7 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

14 The method of claim 9 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

15. A pharmaceutical composition which comprises an amount of the compound of claim 1 effective to inhibit excess matrix metalloproteinas and a pharmaceutically acceptable carrier.

16. A compound of claim 1 for for use as a medicament.

17. Use of a compound of claim 1 for the manufacture of a medicament for inhibiting excess matrix metalloproteinase in a human suffering from or susceptible to a diseases involving connective tissue degradation.

18. The use of claim 17 wherein matrix metalloproteinases comprises collagenases, stromelysins, or gelatinases.

19. The use of claim 17 wherein the disease related to connective tissue degradation is osteoarthrits, rheumatoid arthritis, septic arthritis, osteopenias such as osteoporosis, tumor metastasis (invasion and growth), periodontitis, gingivitis, corneal ulceration, dermal ulceration, or gastric ulceration.

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